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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/435,249	11/05/1999	JAY S. SCHNEIDER	SCH01.NP001	4962

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EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	09/435,249	SCHNEIDER, JAY S.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11-10-2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9-12 and 38-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 9-12, 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

The objection to claim 37, set forth in the prior Office action mailed 05-07-2003 is withdrawn in response to Applicant's amendments filed 11-10-2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4 and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-4 recite the limitation "the isoform" in the first line of each claim. There is insufficient antecedent basis for this limitation in the claims because they depend from claim 1, which does not recite an isoform.

Claims 10-12 recite the limitation "the isoform" in the first line of each claim. There is insufficient antecedent basis for this limitation in the claims because they depend from claim 9, which does not recite an isoform.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 9-12, and 38-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1-4, 9-12 and 38-41 are drawn to methods of treating Parkinson's disease and method of downregulating glutamic acid decarboxylase in a mammal in vivo, wherein an antisense is administered to the mammal via a cannula wherein the antisense comprises SEQ ID NO: 3 and 4. The originally filed specification does not appear to have any support for the claimed methods wherein the antisense used in these methods comprises SEQ ID NO:3 and 4. The originally filed claims are not directed to any specific antisense sequences, but rather are directed to general methods using antisense. The originally filed specification makes reference to SEQ ID NO:3 and 4 sequences used to generate human GAD_{65} and human GAD_{67}, respectively, (See for example, page 8, lines 19-22) which seems to indicate that these sequences were comtemplated as primers. Reference to these sequences (SEQ ID NO:3 and SEQ ID NO:4) as antisense molecules for use in the claimed methods could not be found, nor is it clear that the specification actually contemplated sequences comprising SEQ ID NO:3 or 4 as antisense sequences for use in the claimed methods and, therefore, these limitations are considered to be new matter.

The rejection of record of claims 1-4, 9-12, 30 and 34-37 under 35 U.S.C. 112, first paragraph, as lacking adequate written description, set forth in the prior Office action mailed 05-07-2003, is withdrawn in response of the recitation of the structure of specific antisense sequences, SEQ ID NO: 1-5, in the claimed methods in association with a specific activity for those antisense molecules (i.e. treatment of Parkinson's and downregulation of the expression of glutamic acid decarboxylase in vivo). However, the rejection of record of the claimed methods under 35 USC 112, first paragraph, for lack of enablement is maintained, for the reasons set forth below.

Claims 1-4, 9-12 and 38-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating Parkinson's disease in rat comprising administration of the antisense of instant SEQ ID NO:1 via administration to the substantia nigra pars reticulata via a cannula, and methods of treating Parkinson's disease in monkey comprising administration of the antisense of instant SEQ ID NO:5 via administration to the internal globus pallidus via a cannula, does not reasonably provide enablement for treatment of Parkinson's disease or downregulating glutamic decarboxylase in a mammal in vivo by administration of SEQ ID NO:1 or 5 to mammals other than rat and monkey (respectively), as instantly claimed, nor does it reasonably provide enablement for the claimed methods wherein the antisense administered

comprises SEQ ID NO:2-4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claim 1 is drawn to a method of treatment of Parkinson's disease in any mammal, comprising administering a therapeutically effective amount of antisense oligonucleotide comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5 to the substantia nigra pars reticulata via a cannula for the down regulation of glutamic acid decarboxylase. Claim 2 specifies that the isoform of glutamic acid decarboxylase is GAD_{65}. Claim 3 specifies that the isoform of glutamic acid decarboxylase is GAD_{67}. Claim 4 specifies that the isoform of glutamic acid decarboxylase is a combination of GAD_{65} and GAD_{67}.

Claim 9 is drawn to a method of treatment of Parkinson's disease in any mammal, comprising administering a therapeutically effective amount of antisense oligonucleotide comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5 to the internal globus pallidus via a cannula for the down regulation of glutamic acid decarboxylase. Claim 10 specifies that

the isoform of glutamic acid decarboxylase is GAD_{65}. Claim 11 specifies that the isoform of glutamic acid decarboxylase is GAD_{67}. Claim 12 specifies that the isoform of glutamic acid decarboxylase is a combination of GAD_{65} and GAD_{67}.

Claims 38-41 are drawn to a method of down regulating glutamic acid decarboxylase in any mammal *in vivo*, comprising administering an antisense oligonucleotide directed to an initiation codon of glutamic acid decarboxylase mRNA to the substantia nigra pars reticulata or internal globus pallidus via a cannula, wherein said antisense oligonucleotide comprises SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5. These methods of downregulating glutamic decarboxylase in a mammal in vivo, as claimed, are disclosed in the specification for the express purpose of treating Parkinson's disease and, therefore, have been evaluation for enablement based on this disclosed use.

The specification as filed teaches by way of example administration of antisense to GAD_{67} to rats or monkeys given unilateral lesions of the nigrostraiatal dopamine system using the neurotoxin 6-hydroxdopamine-hydrobromide (6-OHDA-HBr) to experimentally induce parkinsonism. Specifically via administration of instant SEQ ID NO:1 (targeted to rat GAD_{67}) to the substantia nigra pars reticulata (5.3 mm behind bregma, 2.5mm lateral to the midline, 8.2 mm below the skull surface) in rats and via administration of instant SEQ ID NO:5 (targeted to monkey GAD_{67}) to dual cannulae overlying the internal segment of the globus pallidus bilaterally in squirrel monkeys. The specification demonstrates the use of SEQ ID NO:1 and SEQ ID NO:5 in these model systems

for Parkinson's disease resulted in a treatment effect wherein a lessening of akinesia and bradykinesia occurred.

The specification as filed teaches on pages 8-10 that instant SEQ ID NOS. 1 and 2 are rat sequences, SEQ ID NO:1 to rat GAD_{67} and SEQ ID NO:2 to rat GAD_{65}, that instant SEQ ID NOS: 3 and 4 are sequences used to generate the human GAD_{65} and human GAD_{67} sequences, respectively, and the instant SEQ ID NO:5 is an antisense molecule targeted to squirrel monkey GAD_{67}. The specification teaches that these sequences are all directed to the initiation of translation region of the rat, human and monkey GAD_{65} and GAD_{67} gene sequences. The specification also states on page 9, line 15, that "[t]he results of this search indicated that the oligos were only homologous with the genes they were directed against." The specification further relates some of the homology among the different species and isoforms of GAD.

The specification, as filed, has not demonstrated that SEQ ID NO: 1 or 5 are capable of downregulating the expression of any other form of GAD, for example, the specification does not demonstrate that SEQ ID NO:1 or 5 bind to and inhibit the expression of any other species of GAD under physiological conditions, or if such inhibition occurs that the inhibition would occur at a level comparable to the degree of inhibition of the target species. Given that there is only partial sequence homology between the various species of disclosed GAD in the region targeted by SEQ ID NO:1 or 5, the skilled artisan would not predict that SEQ ID NO:1 or 5 would bind and inhibit the expression of any other species of GAD, or that the degree of inhibition would comparable to the inhibition of a

GAD sequence that is fully complementary to SEQ ID NO:1 or 5. The skilled artisan would not predict, without a demonstration of a correlating degree of inhibition, that results shown for SEQ ID NO:1 and 5, as used in the model rat and monkey system to treat Parkinson's disease would correlate for a similar treatment effect for other species. For example, Branch (TIBS 23, cited in prior Office actions) discuss how antisense molecules have been shown to selectively inhibit one form of a gene over another form of a gene wherein there is a single base mismatch (see for example, page 48, first column).

The specification as filed has not shown any down regulation of GAD_{65} in any species, except prophetically, nor has the specification demonstrated a correlation between the treatment effects observed for Parkinson's disease that result from downregulation of GAD_{67} with similar effects from downregulation of GAD_{65}. As discussed in McCarthy et al. (Brain Research, 1994, of record), particularly on page 218, GAD_{67} and GAD_{65} are distinct proteins, with variations in their physiological roles, timing of expression and rate of degradation; these distinct roles have not been fully defined in the art. It is unclear that the treatment effects for Parkinson's disease observed for downregulation of GAD_{67} as demonstrated in the specification, would predictably correlate with similar treatment effects resulting from a downregulation of GAD_{65}, as claimed.

The specification has not actually demonstrated that the specific sequences in the claimed methods, SEQ ID NO: 2-4 actually have antisense activity under the conditions the physiological conditions that occur in the brain in vivo, as would be required for the claimed methods to successfully treat

Parkinson's disease or downregulate expression f the target GAD molecule. For example, there is no guidance in the specification to suggests that SEQ ID NO:2-4 are capable of downregulating the expression of their target GAD in vivo in a mammalian brain and to a degree that GAD expression would be inhibited to a level effective to result in a treatment effect for Parkinson's disease. As discussed, for example, in Branch and Agrawal et al. (Molecular Medicine Today, February 200, cited in prior Office actions), it is unpredictable to determine the ability of an oligonucleotide to inhibit the expression based purely on complementarity to a target mRNA. For example, dependent on the mRNA, different regions of the sequence are accessible to antisense, particularly in vivo, wherein proteins often block access to some regions of an mRNA, and further, in vivo, oligonucleotides of variant sequence are more or less susceptible to non-specific effects, for example, protein binding. As discussed in these references, activity of an antisense molecule is unpredictable and must be determined empirically. Based on the guidance in the specification, the skilled artisan would not predict that any of SEQ ID NO:2-4 actually have the ability to inhibit the expression of their target GAD isoform in vivo, under the physiological conditions in the brain, to a level required to achieve the therapeutic outcomes claimed and encompassed in the claimed methods. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who

teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract)

The filed of antisense recognized that at the time of filing, and even to date, in vivo applications of antisense, particularly for therapeutic purposes, was highly unpredictable, as discussed for example, in Branch, Agrawal, Green et al. (J. Am. Coll. Surg., 200, of record) and Jen et al. (Stem Cells, 2000, of record). Although many of the hurdles for the applications of antisense discussed in these references are related to delivery, which is overcome by the direct delivery provided in the claimed methods by using a cannula, other factors discussed are still relevant to the claimed methods, in light of the very sparse guidance provided in the specification for SEQ ID NO:2-4. For example, Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects." It is unclear that the specific sequences claimed, SEQ ID NO:2-4, would predictably target and inhibit GAD mRNA in vivo and that non-specific effects would not occur, for example, non-specific protein binding, and

that any therapeutic efficacy would result. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

Additonally, the specification has not provided any guidance on the efficacy of the uptake of SEQ ID NO:2-4 in the target cells. It is unpredictable that the uptake of SEQ ID NO:2-4 would correlate with that of the two exemplified embodiments, SEQ ID NO:1 and 5. For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." The guidance provided in the

specification for the uptake of SEQ ID NO:1 and 5 would not provide general guidance for the delivery of SEQ ID NO:2-4, as claimed, given that individual nucleic acids encompassed by the claims would vary in structure (e.g. sequence) and would not be predicted to behave the same as the two embodiments in the specification. This aspect of unpredicatable and variable uptake for antisense has been specifically recognized for the brain, for example, McCarthy et al. (Brain Research, 1994, of record) discuss generally the application of antisense in the brain (starting on p217, section 4.3) and in relation to GAD_{67} and GAD_{65} antisense, and taught the unpredictability in the art for design and use of antisense to GAD_{65} and GAD_{67} in the brain. They teach that "[t]he use of antisense technology in behavioral neurobiology is emerging as a useful investigative tool but limitations of the method are also becoming increasingly apparent." Some of these problems they list are entrance of the antisense into the desired cell (uptake), toxicity, non-specific binding to other initiation start codon regions, and the unpredictability of non-specific effects depending on which route of administration is used: "In the current experiments some behavioral effects of the control oligo were observed. However, nonspecific effects of the control oligo were of a greater magnitude when delivered to the HYP versus the MCG, and not observed at all in the POA." Although they are discussing the specific areas of the brain targeted in their research (HYP, MCG, and POA), similar unpredictability would be expected in brain cells in other parts of the brain.

To practice the claimed methods wherein the antisense administered is SEQ ID NO:2, 3, or 4, the skilled artisan would need to undergo undue trial and error experimentation, and even through such undue experimentation would not predictably expect to be able to successfully practice the claimed methods, wherein the expression of GAD was downregulated and a treatment effect would be achieved for Parkinson's disease. While the specification as filed teaches the administration of instant SEQ ID NO:1 to rat and administration of instant SEQ ID NO:5 to monkey to specific brain regions for a desired treatment effect, such evidence does not provide to one of skill in the art how to use SEQ ID NO:2-4 for administration to any mammal via administration to any brain region, for the claimed methods of down regulation of the GAD and treatment effects for Parkinson's. The results observed for SEQ ID NO:1 and 5 would not be predicted to correlate with results in other mammals, wherein SEQ ID NO: 1 and 5 are not fully complementary to the GAD target and, therefore, may not be inhibited by SEQ ID NO:1 or 5, or may not be inhibited to a degree that is sufficient to result in the observed treatment effects for Parkinson's disease. Further, these results would not be expected to correlate with results for SEQ ID NO:2 and 3, since these target a different and distinct isoform of GAD (GAD_{65}, rather than GAD_{67} as exemplified). It is unclear if the downregulation of GAD_{65} produces the same therapeutic outcome as downregulation of GAD_{67}, since these isoforms are known to have different physiological roles. Further, none of SEQ ID NO:2-4 have been shown to have any antisense activity, or antisense activity effective enough to sufficiently down regulate the target GAD expression

to a level that would produce a therapeutic effect. In particular, the specification does not even seem to identify SEQ ID NO: 3 and 4 as antisense sequences, but rather as sequences used to generate human GAD_{65} and human GAD_{67}, respectively, (see for example, page 8, lines 19-22) which seems to indicate that these sequences were comtemplated as primers. Vased soley on complementarity, it is unpredictable that these sequences would even act as antisense, as discussed above. Each potential antisense must be considered on an antisense-by-antisense basis for its use *in vivo* in view of the high level of unpredictability in the antisense art for the unpredictable factors argued above. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

Applicant's arguments filed December 11, 2003 have been fully considered but they are not persuasive. Applicant provides arguments in response to the rejection of record of claims 1-4, 9-12, 30 and 34-37, as set forth in the prior Office action. These arguments have only been considered to the extent that they are applicable to the new rejection under 35 USC 112, first paragraph, set forth in the instant Office action.

Applicant argues that animal studies are not required to enable an invention, and that the Examiner has not provided any reason to doubt that all of SEQ ID NO:1-5 can be used to inhibit GAD or treat Parkinson's disease. This is

not persuasive because the Examiner is not requiring animal studies, however, the Examiner has pointed out valid reasons why clinical applications for antisense are unpredictable and provided scientific reasoning as to why the examples provided in the specification for SEQ ID NO:1 and 5 would not be taken by the skilled artisan to reasonable correlate for SEQ ID NO:2-4.

Applicant argues that there is sequence homology among the disclosed species of GAD genes surrounding the start site and that the claimed oligonucleotides would be expected to inhibit different GAD isoforms. This is not found to be persuasive, because even with some degree of homology, antisense with less than full complementary to a target region would not be expected to inhibit the expression, or provide an inhibition comparable to that observed for a fully complementary mRNA or if that inhibition would be sufficient to produce the downregulation and treatment effects claimed. For example, as pointed out in the rejection of record, Branch discusses how the specificity of antisense can provide selective inhibition between two sequences differing by as little as one base.

Applicant argues that the similar composition of the claimed antisense would result in similar physical-chemical characteristics; however, even small changes in the composition of a sequence can change the efficacy and uptake of an oligonucleotide (see for example, as discussed in the rejection of record, as discussed by Agrawal et al.).

Applicant argues that Jen et al. is not relevant because the present claims do not require any level of clinical efficacy. This is not persuasive because

claims are still directed to treatment effects for Parkinson's disease and the in vivo downregulation methods are only disclosed in the specification for use in treating Parkinson's disease and, therefore, encompass methods wherein a treatment effect is obtained.

Applicant's arguments directed to Green et al. do not appear relevant to the newly applied rejection under 35 USC 112, first paragraph.

Applicant argues that Agrawal et al. is only directed to problems that occur due to systemic or oral administration of antisense. As applied in the new rejection under 35 USC 112, first paragraph, Agrawal is cited to support the variation of uptake of oligonucleotides, to support that the results for SEQ ID NO:1 and 5 would not be expected to correlate with the uptake for SEQ ID NO:2-4. Applicant's arguments are not addressed to this aspect of the rejection.

Applicant argues that McCarthy et al. does not support the unpredictability of antisense, but rather, supports that antisense applications in the brain can be successfully practiced. This is not found to be persuasive because McCarthy et al. points to many obstacles that exist for antisense applications in the brain. Through empirical experimentation, McCarthy has developed methods wherein they have overcome many of these obstacles, however, the guidance provided in the instant specification has not demonstrated how the oligonucleotides SEQ id NO:2-4 overcome these obstacles. In order to practice the claimed invention, the skilled artisan would need to undergo undue trial and error experimentation to overcome these obstacles for the specifically claimed oligonucleotides SEQ ID NO:2-4, for the treatment methods claimed. Given the unpredictability of

antisense and the lack of guidance in the specification, particularly with regard to the ability of the specifically claimed sequences SEQ ID NO:2-4, it is unclear that even with such undue experimentation, the skilled artisan would actually achieve the outcome of downregulation and treatment required in the claimed methods.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (571) 272-0759. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Lacourciere
March 3, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER